REMARKS

In this communication, claims 8, 9, 13 and 14 have been amended; claims 10-12 have been canceled without prejudice or disclaimer; and new claims 15-17 have been added. The amendments add no new matter and are fully supported by the specification and claims as originally filed. Upon entry of the present amendment, claims 8, 9, and 13-17 will be pending in this application.

Rejection under 35 U.S.C. §101

Applicants respectfully traverse the rejection of claims 8 and 14 under 35 U.S.C. §101 as allegedly containing unpatentable subject matter.

The Office Action alleges that claims 8 and 14 are broadly drawn to polyclonal antibodies that bind to any heparin-binding growth factor polypeptide as found in nature. Without acquiescing to the rationale provided in the Office Action, and in order to expedite prosecution, Applicants have amended the claims to recite that the antibody is "isolated" rendering the rejection moot.

Accordingly, Applicants request withdrawal of the rejection.

Rejections under 35 U.S.C §112, Second Paragraph

Applicants respectfully traverse the rejection of claims 9 and 11-14 under 35 U.S.C. §112, second paragraph as allegedly being indefinite. Claims 11 and 12 have been canceled rendering the rejection moot as to such claims.

With regard to claim 9, the Office Action alleges that recital of the term "has" is indefinite because the phrase may mean either "consists of", or alternatively "comprises". Without acquiescing to the rationale provided in the Office Action, and in order to expedite prosecution of the instant application, Applicants have amended the claims by deleting the term "has" rendering the rejection moot.

Accordingly, Applicants request withdrawal of the rejection.

With regard to claims 13 and 14, the Office Action alleges that recital of the phrase "or antibody fragment thereof" is indefinite since an antibody cannot be a fragment of itself. Without acquiescing to the rationale provided in the Office Action, and in order to expedite prosecution of the instant application, Applicants have amended the claims by deleting the phrase "or antibody fragment thereof" rendering the rejection moot.

Accordingly, Applicants request withdrawal of the rejection.

Provisional Nonstatutory Double Patenting Rejection

In the Office Action, claims 8-14 were provisionally rejected on the ground of non-statutory double patenting over claims 15, 19, and 21 of co-pending Application No. 10/658,856 (hereinafter, the `856).

According to the Manual of Patent Examining Procedure (MPEP) §804, the issue of double patenting is only considered when two or more patents or applications have at least one common inventor and/or are either commonly assigned/owned or non-commonly assigned/owned but subject to a joint research agreement as set forth in 35 U.S.C. 103(c)(2) and (3) pursuant to the CREATE Act (Pub. L. 108-453, 118 Stat. 3596 (2004)). (MPEP 8th Edition, August 2001; latest revision July 2008.)

As the present application and the `856 do not have a common inventor and are not commonly assigned or subject to a research agreement, the rejection is not proper. Applicants further note that as the `856 was filed after the filing of the present application, the `856 does not serve as prior art to the present application.

Accordingly, Applicants request withdrawal of the rejection.

Rejections under 35 U.S.C §102

Applicants respectfully traverse the rejection of claims 8, 10, 13 and 14 under 35 U.S.C. §102(e), as allegedly anticipated by Jaye et al. (U.S. Patent No. 4,868,113).

To anticipate, a single reference must inherently or expressly teach each and every element of the claimed invention. *In re Spada*, 15 USPQ2d 1655 (Fed Cir. 1990); and *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131.

Without acquiescing to the rationale provided in the Office Action, and in order to expedite prosecution of the instant application, Applicants have amended the claims to further define the sequence of the HBGF polypeptide to which the antibodies of the claims bind. Specifically, claim 8 has been amended to include the limitation of claim 9, which has not been rejected in view of Jaye et al. Applicants respectfully submit that Jaye et al. fail to disclose a polypeptide having the specific sequence recited in the amended claims and therefore, Jaye et al. fail to anticipate the claimed invention.

Accordingly, Applicants request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 8-14 under 35 U.S.C. §102(e), as allegedly anticipated by Frank et al. (U.S. Patent No. 5,795,862).

Frank et al. disclose a fragment of an Ectoparasite saliva protein, which fragment has a sequence (SEQ ID NO: 31) which shares 6 amino acids in common with the sequence of SEQ ID NO: 2. The Examiner states that Frank also discloses antibodies (Col. 4, lines 16-18). The Office Action alleges that the sequences of SEQ ID NO: 2 and SEQ ID NO: 31 are sufficiently similar that it would be expected that the antibodies of Frank et al. would bind to the HBGF polypeptides comprising SEQ ID NO: 2 and thereby meet the limitation of the antibodies as presently claimed.

According to the MPEP §2112(IV), "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." See, *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666

F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). Further, "to establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient'." *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)

The region of a protein to which an antibody binds is called an epitope. The epitope can either be continuous (*i.e.*, linear) or discontinuous. Most epitopes are discontinuous and are composed of amino acids from different regions along the linear sequence of the protein that are brought together in space by the folding of the protein. Discontinuous epitopes may consist of 15-22 amino acids. Although about 10% of epitopes are continuous, the ability of any particular linear sequence to serve as an epitope depends on several parameters including the hydrophilicity, flexibility, accessibility, exposed surface, polarity, and antigenic propensity of the particular linear amino acid sequence. Various analytical methods have been developed to predict linear epitopes within an amino acid sequence. (See, e.g., Larsen et al. (2006) Improved method for predicting linear B-cell epitopes. Immunome Res 2:2; and Kolasker and Tongaonkar (1990) A semi-empirical method for prediction of antigenic determinants on protein antigens. FEBS Lett 276:172-4.)

Frank et al. provides flea saliva proteins, protein fragments, and nucleotides encoding those proteins. One such flea saliva protein fragment disclosed by Frank et al. is SEQ ID NO: 31, which is 25 amino acids in length. The HBGF polypeptides of the present invention are 102-103 amino acids in length, comprise N-terminal sequences of SEQ ID NO: 1 and/or SEQ ID NO: 2, and are fragments

of a mammalian protein. An alignment of SEQ ID NO: 31 of Frank et al. and SEQ ID NO: 1 and SEQ ID NO: 2 of the present application is shown below.

DIENIKKGEGQPGAPGGKENNLSV	SEQ ID NO:31 (Frank et al.)
EENIKKGKKXIRT	SEQ ID NO:1
ENIKKGKKXIRT	SEQ ID NO:2

Sequence identity between SEQ ID NO:31 and SEQ ID NO:1, SEQ ID NO:2, and the HBGF proteins presently claimed, consists solely of the 6 amino acid sequence ENIKKG. As stated above, six amino acids represents the very lower limit for the size of a linear epitope, and would require optimal orientation, accessibility, and charge distribution to function as an antibody binding site. Analysis of SEQ ID NO: 31 of Frank et al. and SEQ ID NOs: 1 and 2 of the present invention using analytical methods including Larsen et al. (*supra*) and Kolasker and Tongaonkar (*supra*) as provided, e.g., at the website http://tools.immuneepitope.org/main/, does not predict that the six amino acid sequence ENIKKG, in either the context of SEQ ID NO: 31 or SEQ ID NOs: 1 and 2, would serve as a continuous epitope. Thus, in the absence of evidence that an antibody that binds to the sequence ENIKKG and binds to both SEQ ID NO: 31 and the HBGF polypeptides presently claimed is inherently included in Frank et al., one of skill would not reasonably conclude that Frank et al. anticipates the present claims.

Moreover, Frank does not disclose any particular isolated antibodies to Ectoparasite saliva proteins, any particular isolated antibodies to the fragment of sequence SEQ ID NO: 31, or any particular isolated antibodies that recognize the 6 common amino acids ENIKKG. What Frank describes are antibodies that are *capable of selectively binding* to an Ectoparasite saliva product (Col 4, lines 16-18). Applicant contends that the antibodies that are capable of selectively binding to an Ectoparasite saliva protein would not be ones which also specifically bind to a HBGF protein (as required in the present invention). The antibodies described in Frank therefore do not anticipate the presently claimed antibodies.

Accordingly, Applicants request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 8-14 under 35 U.S.C. §102(b), as allegedly anticipated by Grotendorst et al. (U.S. Patent No. 5,408,040). Claims 11 and 12 have been canceled rendering the rejection moot as to such claims.

Grotendorst et al. disclose CTGF and claim a genus of antibodies that bind CTGF. No species were disclosed. According to the MPEP, a genus does not always anticipate a claim to a subgenus or species within the genus.

> When the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated. Ex parte A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990).

MPEP §2131.02. As discussed in detail above, the HBGF polypeptides described in the specification and recited in the claims are "microheterogenous forms of truncated CTGF" (see, for example, page 28, line 10 of the specification as filed) and correspond to amino acids 247-349 and 248-349 of the CTGF polypeptide as defined in SEQ ID NO: 2 of Grotendorst et al. The antibodies that bind to HBGF are a subgenus of antibody not specifically described or exemplified by Grotendorst. The present inventors have discovered that HBGF represents a naturally-occurring variant of CTGF and that antibodies specifically targeting HBGF are particularly useful in inhibiting activities associated with these fragments.

Further, in view of the differences in the primary structure of the full length CTGF polypeptide defined by SEQ ID NO: 2 of Grotendorst et al. with the HBGF polypeptide of the claims (*e.g.*, about 100 amino acids and about 349 amino acids, respectively) and the dependence of secondary and tertiary structure on the primary structure, particularly that associated with disulfide bond formation, it is submitted that antibodies of the presently amended claims may differ from those disclosed in Grotendorst et al. Applicants respectfully submit that Grotendorst et al. fail to disclose

the specific polypeptides recited in the claims and species of antibodies that bind to said fragments. Therefore, Grotendorst et al. fail to anticipate the claimed invention.

Accordingly, Applicants request withdrawal of the rejection.

Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

Please charge Deposit Account No. 07-1896 in the amount of $960.00 to cover a Three Month Extension of Time fee and a Request for Continued Examination fee. No additional fees are deemed necessary with the filing of this paper. However, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896, referencing the above-identified docket number.

Respectfully submitted,

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